

## Plasma levels after a single oral dose of 1.5 g ornidazole

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**SUMMARY** Administration of a single oral dose of 1.5 g ornidazole to volunteers produced plasma levels which remained above the mean minimal trichomonocidal concentration for between 54 and 72 hours. A subjective feeling of dizziness was observed by all volunteers, but it was not possible to make a correlation between this and the drug levels in this study.

### Introduction

Several 5-nitroimidazoles, such as metronidazole and tinidazole, have been shown to produce a strong clinical response in trichomoniasis when given as a single 2 g oral dose (Csonka, 1971; Woodcock, 1972; Røseman and Vaughan, 1973; Milek and Nedelkova, 1974). Similar results have also been obtained with ornidazole\*, a potent new trichomonocidal drug (Siboulet, 1975; Nygaard *et al.*, 1977). In previous studies (Schwartz and Jeunet, 1976a) ornidazole was shown to have a longer half-life (14.4 h) than metronidazole (8.4 h). Other studies (Schwartz and Jeunet, 1976b) indicated that ornidazole is well absorbed from the vagina and that such application in addition to an oral dose allows the plasma levels of the drug to be maintained above the minimal inhibitory concentration (MIC) for a longer period of time. Since the high doses (2 or 3 g) of ornidazole used in these studies often produced side effects, we wondered if the side effects could be lessened by lowering the dose.

In the present study plasma levels of ornidazole, after administration of a 1.5 g oral dose (three Tiberal Roche tablets of 500 mg) were determined. Additionally, an attempt was made to see whether there was any relationship between the plasma levels and the occurrence of side effects.

### Material and methods

Five healthy volunteers, women aged between 20 and 28 years and weighing 47 to 60 kg, were used in our study after their consent had been obtained. They were told not to take alcohol, barbiturates, or other known enzyme inducers during the 14 days preceding the study. Neither drugs nor alcohol was allowed during the study.

The women arrived at the hospital at 7.30 a.m. A standard breakfast consisting of toast without butter, marmalade and tea or coffee was served between 7.30 and 7.45. Three tablets of 500 mg ornidazole\* were swallowed at 8.00 a.m. with 100 ml of water.

Blood samples of 10 ml were taken using a Venject† at 0, 1, 2, 3, 4, 5, 6, 12, 24, 48, and 72 hours after swallowing the tablets. If a subject complained of a side effect, an additional blood sample was taken immediately.

The volunteers were asked to avoid strong physical activity. Lunch without fat or milk was served at noon and dinner between 4.0 and 5.0 p.m. At regular intervals at the times of blood sampling each woman was asked if she had any discomfort, and any complaint was noted. If discomfort was being experienced the woman would describe it without knowing what side effect might be expected. Each was told not to discuss symptoms between themselves, but only with the physician.

\* $\alpha$ -(chloromethyl)-2-methyl-5-nitroimidazole-1-ethanol.

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After centrifugation plasma was separated and stored in a freezer at  $-18^{\circ}\text{C}$ . Plasma samples were analysed for their content of unaltered ornidazole, using pulse polarography after thin layer chromatographic separation, as described by de Silva *et al.* (1970). Sensitivity limit of the method is 0.2–0.3  $\mu\text{g/ml}$ .

## Results

### PLASMA CONCENTRATIONS

The plasma values of ornidazole measured in the five volunteers are shown in Table 1 and the Figure. Individual peak concentrations ranging between 31.5\* and 36.3  $\mu\text{g/ml}$  (mean = 33.2  $\mu\text{g/ml}$ ) were observed within two hours of administration.

After four hours a plateau was often observed in the plasma profile. The mean plasma half-life ( $\pm$  SD) determined between 6 and 48 hours after administration, when the semilogarithmic course of the plasma curves was linear, was  $13.8 \pm 1.8$  hours. Individual half-lives of elimination and elimination constants are given in Table 1.

### SIDE EFFECTS

All the women suffered various degrees of dizziness

\*Subject 3 is not included, because the sample after 1 hour was lost, thus we do not know the peak concentration.

between 15 and 30 minutes after administration (Table 2). The table also gives the concentration of ornidazole measured in the plasma after these side effects were observed. In three of the subjects it was possible to take a blood sample within 11 minutes of dizziness. These samples showed concentrations ranging between 20.4 and 30.2  $\mu\text{g/ml}$ . Dizziness lasted for approximately one hour in three of the women and  $1\frac{1}{2}$  hours and 3 hours in the other two.

## Discussion

### PLASMA CONCENTRATIONS

The observed plateau in plasma profiles is difficult to interpret. It may indicate enterohepatic circulation, however data on bile concentrations of ornidazole in rats do not support this theory (Richle *et al.*, 1977), and such data are not yet available on man.

The possibility that delayed absorption of one of the three tablets could account for the phenomenon seems unlikely in all five subjects.

When tested *in vitro* against the same strain for *Trichomonas vaginalis*, ornidazole and metronidazole showed a trichomonicidal range of 0.37 to 2.5  $\mu\text{g/ml}$  (mean 1.05) and 0.75 to 5.0  $\mu\text{g/ml}$  (mean 2.12) respectively (Richle *et al.*, 1977). As less than

Table 1 Plasma concentrations ( $\mu\text{g/ml}$ ) of unaltered ornidazole, calculated elimination constants ( $h^{-1}$ ) and plasma half-lives ( $h$ ) after an oral dose of 1.5 g to five female volunteers.

Subject	Hours after administration									Kel (6-48 h)	t½ (6-48 h)
	1	2	3	4	6	12	24	48	72		
1	30.6	36.3	31.2	31.2	24.6	17.5	11.2	3.7	0.8	0.044	15.6
2	30.3	31.5	28.0	28.2	22.5	16.0	10.0	2.8	1.1	0.049	14.1
3	—	27.5	26.3	26.5	22.3	13.0	8.7	2.8	—	0.047	14.7
4	32.0	28.8	26.5	26.6	21.4	11.3	6.9	1.3	0.2	0.064	10.8
5	33.0	31.5	27.5	27.4	24.2	14.5	9.4	2.6	0.9	0.051	13.6
Mean	31.5	31.5	27.9	28.0	23.0	14.5	9.2	2.6	0.8	0.051	13.8
±SD	1.3	3.4	2.0	1.9	1.4	2.4	1.6	0.9	0.4	0.0077	1.8

Table 2 Plasma concentrations measured after occurrence of side effect and plasma concentrations extrapolated at disappearance of side effect, after an oral dose of 1.5 g to five female volunteers.

Subject	Age (years)	Weight (kg)	Height (cm)	Appearance of side effects					Disappearance of side effects	
				Type	Presence after administration (min)	Time between sample and administration (min)	Measured concentration ( $\mu\text{g/ml}$ )	Duration (hours)	Approximate concentration ( $\mu\text{g/ml}$ )	
1	20	52	164	Dizzy	28	30	20.4	1	33	
2	28	55	161	Dizzy	15	34	28.9	1	30	
3	22	60	164	Dizzy, sweating	30	38	20.4	$1\frac{1}{2}$	27	
4	24	47	164	Very dizzy	30	41	30.2	1	30	
5	23	57	165	Dizzy, slacky	15	69	33.0	3	27	

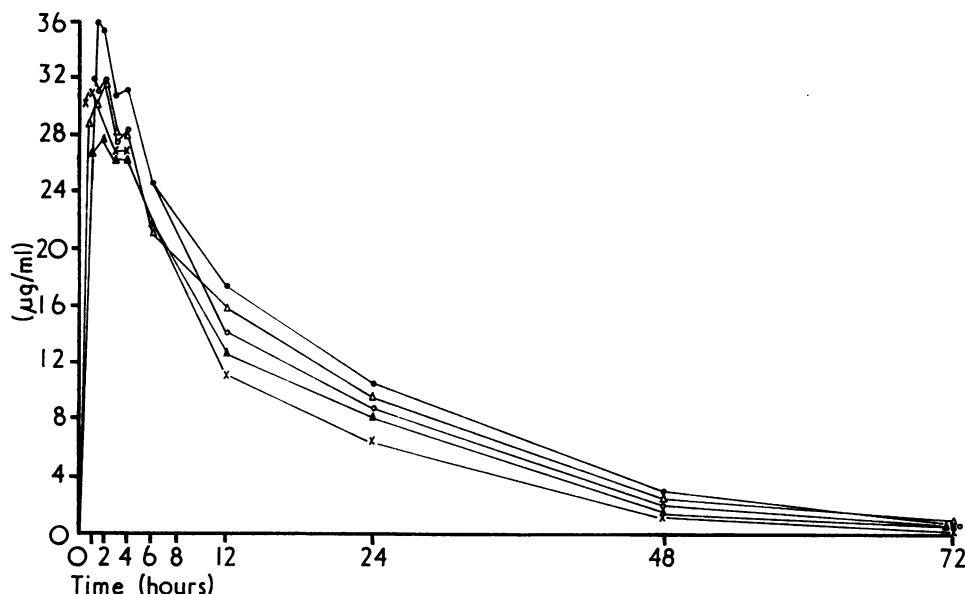


Figure Plasma concentrations ( $\mu\text{g/ml}$ ) of ornidazole after an oral dose of 1.5 g to five female volunteers.

13.4% of the drug is bound to plasma proteins (Schwartz and Jeunet, 1976a), minimal trichomonocidal concentrations (MCC) in plasma should not be affected.

Plasma levels of unchanged ornidazole, as measured in the present study, were found to remain above the trichomonocidal range ( $> 2.5 \mu\text{g/ml}$ ) for 48 hours with the exception of subject 4. Plasma levels remained above the mean MCC ( $= 1.05 \mu\text{g/ml}$ ) for between 54 and 72 hours. The ornidazole levels in vaginal fluid and their correlation to plasma levels have not yet been determined, and it is not possible therefore to conclude that the measured plasma levels are sufficient to cure trichomoniasis. However, in a controlled clinical trial performed by Hillström *et al.* (1977) all patients were cured using this dose.

Plasma levels after a 2 g oral dose of ornidazole have been found to remain above MIC for at least 36 hours (Sköld, *et al.*, 1977).

The discrepancy between our results and theirs is partly explained by their MIC value measured at  $5.0 \mu\text{g/ml}$ , and partly by the shorter half-life they found ( $12.6 \text{ hours} \pm 1.1$ ), but it is still noticeable that plasma peak levels after 2 g ornidazole were within the same limits as they were after 1.5 g ornidazole. It should be pointed out that two different chemical methods for determination of unchanged ornidazole in plasma have been used in these studies.

Because of its shorter half-life metronidazole given in a 2 g oral dose produces serum levels above the MCC for a shorter period of time (at least 24 hours) as reported by Woodcock, 1972.

Forsgren and Wallin (1974) measured serum levels of tinidazole in four volunteers after a 2 g oral dose. They found that serum levels remained for 48 hours above the MCC for most of the isolated strains.

#### SIDE EFFECTS

A feeling of dizziness was reported by all volunteers 15–30 minutes after taking the tablets. At this point plasma levels were approximately  $20 \mu\text{g/ml}$ . Approximate concentrations measured when the side effect had disappeared were higher (between  $33.5^* \mu\text{g/ml}$  and  $27.5^* \mu\text{g/ml}$ ). These data together with the fact that we studied only five subjects do not allow us to suggest that there is any correlation between plasma levels and the presence of side effects. This may indicate that the side effects are elicited by the rapid increase of ornidazole *per se* in the target organs, similar to what may be observed with other substances (Alvan *et al.*, 1974). A slow release formulation of the drug would perhaps give fewer side effects.

In view of the unusually high incidence of complaints, it should be pointed out that the drug is

\*Interpolated figures.

usually recommended to be taken during the evening after a meal before going to bed. In this study the tablets were taken at 8.00 a.m. by healthy volunteers, and it is not unlikely that they will be more susceptible to any kind of discomfort. The incidence of side effects has recently been evaluated in a double-blind study (Hillström *et al.*, 1977) using 1.5 g ornidazole and 2 g tinidazole. Side effects were found to be present in six out of 45 patients and in nine out of 43 patients respectively.

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